Intracellular traffic jam : cholesterol accumulation as cause for chronic inflammatory diseases

Valorisation

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Societal relevance

NASH is a disease frequently associated with obesity. In Western countries it is becoming increasingly prevalent and is even seen in children. The current prevalence of NASH within the general population is estimated to be as high as 2-3%. However, among obese subjects the prevalence is much higher and it is estimated to be present in 50-100% of these patients. Furthermore, the number of NASH patients is expected to increase dramatically due to the increasing prevalence of obesity. The propensity of NASH to progress to advanced liver disease is a primary concern. Studies suggest that 16-30% of affected individuals will have a progressive course, resulting in fibrosis and cirrhosis and an increased risk of liver cancer (www.liverfoundation.org). NASH is by far the most prevalent liver disease and is one of the main causes for liver transplantation. In view of the prevalence of NASH, even a low rate of progression to end-stage liver disease has enormous public health implications. Therefore, there is a critical need to improve diagnosis and therapy for NASH. The potential economic impact of our successful data described in this thesis is therefore expected to be exceptionally high. The results obtained are expected to affect a wide area of research related to metabolic syndrome including diabetes and cardiovascular diseases, and fields with similar mechanisms (such as lysosomal storage diseases and alcoholic fatty liver).

Potential clinical relevance

Results found in this thesis have enormous potential clinical relevance. Indeed, our research group has registered 6 patents, partially based on data described in this thesis: two patents related to non-invasive diagnosis of NASH and four others related to the treatment of hepatic inflammation (concerning antibodies against oxLDL, oxysterols, 27HC and NPC). NASH is emerging as a major clinical problem worldwide. In line, several leading pharmaceutical companies have already shown interest in these patents.

Our research is also of relevance to other fields of medicine. In analogy with our novel observations in the liver, much of the cholesterol in foam cells of advanced atherosclerotic plaques appears to be trapped in lysosomes, highlighting the general significance of these observations. It should be noted that the net effect of lysosomal cholesterol accumulation on inflammation in the arteries has never been established. Therefore, as well as contributing to the NASH field, the obtained results are also expected to be highly valuable for future research into cardiovascular diseases, obesity and gut function, including their diagnosis and therapy. Finally, given the general relevance of the mechanistic understanding, linking lysosomal dysfunction to inflammation is also expected to have an important impact in several fields of medicine outside of the metabolic syndrome (i.g. lysosomal storage diseases). In

summary, this thesis will open new avenues for the study of the complex link between lipid metabolism and inflammation, as manifested in the metabolic syndrome.

Originality and/or innovative elements of the topic

In most studies in the fatty liver field, it is the total amount of lipids within the liver that is viewed as a main trigger for inflammation. Yet, this point of view does not explain the lack of correlation between steatosis and inflammation in human NASH. In contrast, my thesis focuses on the intracellular distribution of cholesterol inside Kupffer cells/macrophages. This novel approach is promising since there is a strong correlation between lysosomal cholesterol accumulation in Kupffer cells and hepatic inflammation. This conceptually innovative view on the pathogenesis of NASH predicts that therapy and prevention should not concentrate on fighting steatosis, as stated by current views on the problem, but in contrast should focus directly on lysosomal cholesterol accumulation in Kupffer cells as an initial trigger for inflammation and liver damage. Similarly, reducing plasma lipids levels are currently the main focus for prevention and treatment of atherosclerosis but more focus should be on directly targeting the underling mechanisms for initiation of inflammation. Finally, in contrast to the current non-invasive markers for NASH that focus on liver damage at late stages of the disease, the focus on early events will yield early markers to detect inflammation before substantial liver damage occurred.

Potential applications of results

The involvement of lysosomal cholesterol trapping in macrophages in triggering inflammation makes it an interesting target for the improvement of diagnostic and therapy options in diseases characterized by the presence of chronic inflammation. First of all, data from this thesis indicate the potential of (oxy)sterols to be used as therapy against NASH by stimulating transport of cholesterol from lysosomes to the cytoplasm. Further research has to be performed to translate our findings regarding 27HC to the human situation. As we indicate the potential of diet interventions by adding plant sterol or plant stanol esters to prevent the development of hepatic inflammation, it is of great interest to also study the potential of dietary supplementation of 27HC to reduce hepatic inflammation. Besides that, our data further point towards specifically targeting macrophages in order to improve therapy options. Raising intracellular 27HC levels specifically in macrophages may have great potential in treating NASH. In addition, as we found that inflammasome activation in macrophages plays an important role in both NASH and atherosclerosis, specifically targeting inflammasomes in macrophages or blocking the IL-1 receptor is promising in reducing the inflammatory response. Future studies are needed to identify optimal application conditions of the different modulators described in this thesis.